Complete Summary

GUIDELINE TITLE

Locally advanced (high-risk) prostate cancer.

BIBLIOGRAPHIC SOURCE(S)

Lee WR, Papagikoa MA, Roach M III, Anscher MS, Beyer DC, Lawton CA, Merrick G, Michalski JM, Pollack A, Vijayakumar S, Carroll PR, Higano CS, Mauch PM, Expert Panel on Radiation Oncology-Prostate Work Group. Locally advanced (high-risk) prostate cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 13 p. [49 references]

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Pollack A, Paryani SB, Hussey D, Perez CA, Beyer DC, Blasko JC, Forman JD, Lee WR, Potters L, Roach M, Scardino P, Schellhammer P, Leibel S. Locally advanced (high-risk) prostate cancer. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1401-12.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Locally advanced (high risk) prostate cancer

GUIDELINE CATEGORY

Treatment

CLINICAL SPECIALTY

Internal Medicine
Oncology
Radiation Oncology
Radiology
Surgery

INTENDED USERS

Health Plans
Hospitals
Managed Care Organizations
Physicians
Utilization Management

GUIDELINE OBJECTIVE(S)

To evaluate the appropriateness of radiologic treatment procedures for patients with locally advanced (high risk) prostate cancer

TARGET POPULATION

Patients with locally advanced (high risk) prostate cancer

INTERVENTIONS AND PRACTICES CONSIDERED

1. Androgen ablation mixed with external radiation therapy
    - Combined androgen blockade (CAB) followed by luteinizing hormone-releasing hormone (LHRH)
    - LHRH for life
    - CAB
2. External beam radiation therapy (EBRT) (assumes hormone therapy given)
    - Intensity-modulated radiation therapy (IMRT)
    - Three-dimensional computed tomography (3D-CT)-based plan
    - Two-dimensional computed tomography (2D-CT)-based plan
    - Consideration of pelvic and prostate dose
3. Brachytherapy (assumes hormone therapy given)
    - High-dose-rate (HDR) with EBRT
    - Low-dose-rate (LDR) with EBRT
    - LDR monotherapy
    - HDR monotherapy

MAJOR OUTCOMES CONSIDERED

- Local and distant control rates
- Prostate-cancer-specific and overall mortality

- Disease-free, progression-free, biochemical relapse-free, and 5-year and 10-year overall survival rates

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

The guideline developer performed literature searches of peer-reviewed medical journals and the major applicable articles were identified and collected.

NUMBER OF SOURCE DOCUMENTS

The total number of source documents identified as the result of the literature search is not known.

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Not Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not stated

METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

One or two topic leaders within a panel assume the responsibility of developing an evidence table for each clinical condition, based on analysis of the current literature. These tables serve as a basis for developing a narrative specific to each clinical condition.

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Delphi)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Since data available from existing scientific studies are usually insufficient for meta-analysis, broad-based consensus techniques are needed for reaching agreement in the formulation of the appropriateness criteria. The American

College of Radiology (ACR) Appropriateness Criteria panels use a modified Delphi technique to arrive at consensus. Serial surveys are conducted by distributing questionnaires to consolidate expert opinions within each panel. These questionnaires are distributed to the participants along with the evidence table and narrative as developed by the topic leader(s). Questionnaires are completed by participants in their own professional setting without influence of the other members. Voting is conducted using a scoring system from 1-9, indicating the least to the most appropriate imaging examination or therapeutic procedure. The survey results are collected, tabulated in anonymous fashion, and redistributed after each round. A maximum of three rounds is conducted and opinions are unified to the highest degree possible. Eighty percent agreement is considered a consensus. This modified Delphi technique enables individual, unbiased expression, is economical, easy to understand, and relatively simple to conduct.

If consensus cannot be reached by the Delphi technique, the panel is convened and group consensus techniques are utilized. The strengths and weaknesses of each test or procedure are discussed and consensus reached whenever possible. If "No consensus" appears in the rating column, reasons for this decision are added to the comment sections.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Criteria developed by the Expert Panels are reviewed by the American College of Radiology (ACR) Committee on Appropriateness Criteria.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

ACR Appropriateness Criteria®

Clinical Condition: Locally Advanced (High-risk) Prostate Cancer

Variant 1: Stage T3/T4, PSA <20, Gleason <7.

Treatment	Appropriateness Rating	Comments
Androgen Ablation Mixed with XRT		
CAB followed by LHRH (≥4 and <28 months)	7	
CAB followed by LHRH (≥28 months)	7	
LHRH for life	4	
CAB (<4 months)	3	
External Beam Pelvic Dose (Assumes hormone therapy given)		
<44 Gy	4	
44 Gy to 50.4 Gy	8	
>50.4 Gy	4	
External Beam Prostate Dose (including pelvic dose) (Assumes hormone therapy given)		
<70 Gy	2	
≥70 Gy to <75.6 Gy	7	
≥75.6 Gy	7	
External Beam Treatment Plan (Assumes hormone therapy given)		
IMRT	8	
3D-CT based plan	7	
2D-CT based plan	2	
Brachytherapy (Assumes hormone therapy given)		
HDR with EBRT	7	
LDR with EBRT	6	
LDR monotherapy	2	
HDR monotherapy	2	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 2: Stage T3/T4, PSA <20, Gleason ≥7.

Treatment	Appropriateness Rating	Comments
Androgen Ablation Mixed with XRT		
CAB followed by LHRH (≥28 months)	8	
CAB followed by LHRH (≥4 and <28 months)	7	
LHRH for life	6	
CAB (<4 months)	2	
External Beam Pelvic Dose (Assumes hormone therapy given)		
<44 Gy	4	
44 Gy to 50.4 Gy	8	
>50.4 Gy	4	
External Beam Prostate Dose (including pelvic dose) (Assumes hormone therapy given)		
<70 Gy	2	
≥70 Gy to <75.6 Gy	7	
≥75.6 Gy	7	
External Beam Treatment Plan (Assumes hormone therapy given)		
IMRT	8	
3D-CT based plan	7	
2D-CT based plan	2	
Brachytherapy (Assumes hormone therapy given)		
HDR with EBRT	7	
LDR with EBRT	6	
LDR monotherapy	2	

Treatment	Appropriateness Rating	Comments
HDR monotherapy	2	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 3: Stage T3/T4, PSA ≥20, Gleason <7.

Treatment	Appropriateness Rating	Comments
Androgen Ablation Mixed with XRT		
CAB followed by LHRH (≥28 months)	8	
CAB followed by LHRH (≥4 and <28 months)	7	
LHRH for life	6	
CAB (<4 months)	2	
External Beam Pelvic Dose (Assumes hormone therapy given)		
<44 Gy	4	
44 Gy to 50.4 Gy	8	
>50.4 Gy	4	
External Beam Prostate Dose (including pelvic dose) (Assumes hormone therapy given)		
<70 Gy	2	
≥70 Gy to <75.6 Gy	7	
≥75.6 Gy	7	
External Beam Treatment Plan (Assumes hormone therapy given)		
IMRT	8	
3D-CT based plan	7	

Treatment	Appropriateness Rating	Comments
2D-CT based plan	2	
Brachytherapy (Assumes hormone therapy given)		
HDR with EBRT	7	
LDR with EBRT	6	
LDR monotherapy	2	
HDR monotherapy	2	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 4: Stage T3/T4, PSA ≥20, Gleason ≥7.

Treatment	Appropriateness Rating	Comments
Androgen Ablation Mixed with XRT		
CAB followed by LHRH (≥28 months)	8	
CAB followed by LHRH (≥4 and <28 months)	7	
LHRH for life	6	
CAB (<4 months)	2	
External Beam Pelvic Dose (Assumes hormone therapy given)		
<44 Gy	4	
44 Gy to 50.4 Gy	8	
>50.4 Gy	4	
External Beam Prostate Dose (including pelvic dose) (Assumes hormone therapy given)		
<70 Gy	2	

Treatment	Appropriateness Rating	Comments
≥70 Gy to <75.6 Gy	7	
≥75.6 Gy	7	
External Beam Treatment Plan (Assumes hormone therapy given)		
IMRT	8	
3D-CT based plan	7	
2D-CT based plan	2	
Brachytherapy (Assumes hormone therapy given)		
HDR with EBRT	7	
LDR with EBRT	6	
LDR monotherapy	2	
HDR monotherapy	2	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 5: Stage T1/T2, PSA ≥20, Gleason <7.

Treatment	Appropriateness Rating	Comments
Androgen Ablation Mixed with XRT		
CAB followed by LHRH (≥4 and <28 months)	7	
CAB followed by LHRH (≥28 months)	6	
CAB (<4 months)	3	
LHRH for life	2	
External Beam Pelvic Dose (Assumes hormone therapy given)		

Treatment	Appropriateness Rating	Comments
<44 Gy	4	
44 Gy to 50.4 Gy	8	
>50.4 Gy	4	
External Beam Prostate Dose (including pelvic dose) (Assumes hormone therapy given)		
<70 Gy	2	
≥70 Gy to <75.6 Gy	7	
≥75.6 Gy	8	
External Beam Treatment Plan (Assumes hormone therapy given)		
IMRT	8	
3D-CT based plan	7	
2D-CT based plan	2	
Brachytherapy (Assumes hormone therapy given)		
HDR with EBRT	7	
LDR with EBRT	7	
LDR monotherapy	4	
HDR monotherapy	4	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Variant 6: Stage T1/T2, PSA ≥20, Gleason ≥7.

Treatment	Appropriateness Rating	Comments
Androgen Ablation Mixed with XRT		
CAB followed by LHRH (≥28 months)	8	

Treatment	Appropriateness Rating	Comments
CAB followed by LHRH (≥4 and <28 months)	7	
LHRH for life	6	
CAB (<4 months)	2	
External Beam Pelvic Dose (Assumes hormone therapy given)		
<44 Gy	4	
44 Gy to 50.4 Gy	8	
>50.4 Gy	4	
External Beam Prostate Dose (including pelvic dose) (Assumes hormone therapy given)		
<70 Gy	2	
≥70 Gy to <75.6 Gy	7	
≥75.6 Gy	7	
External Beam Treatment Plan (Assumes hormone therapy given)		
IMRT	8	
3D-CT based plan	7	
2D-CT based plan	2	
Brachytherapy (Assumes hormone therapy given)		
HDR with EBRT	7	
LDR with EBRT	6	
LDR monotherapy	2	
HDR monotherapy	2	
Appropriateness Criteria Scale 1 2 3 4 5 6 7 8 9 1 = Least appropriate 9 = Most appropriate		

Note: Abbreviations used in the tables are listed at the end of the "Major Recommendations" field.

Historical Definition of Locally Advanced Prostate Cancer

"Locally advanced" prostate cancer before the advent of PSA testing typically referred to patients whose prostate tumor on clinical exam or post-prostatectomy histologic examination had disease extend outside the prostatic capsule (T3) or invade adjacent structures (T4). Treatment of these patients with EBRT produced actuarial local control, disease-free, and overall survival rates of 75%, 40%, and 27%, respectively. The most important pretreatment prognostic factors in the pre-PSA era were Gleason score and T-stage. The definition of a "high-risk" patient has evolved over the past decade with the adoption of widespread PSA testing. Pretreatment PSA has joined Gleason score and T-stage as an important independent prognostic factor. Extensive stage migration has occurred with the advent of PSA screening such that the most frequent presenting stage is now clinically nonpalpable (and presumably low-volume) T1c disease. The combined prognostic value of PSA, clinical T-stage, and Gleason score is superior to that of any one of these factors alone and has led to the ability to stratify patients based on pretreatment clinical risk group classifications.

Risk Group Stratification

Risk group stratifications based on pre-treatment PSA, Gleason score, and T-stage have been proposed by several researchers; however, the most widely adopted classification was developed by D'Amico et al. The D'Amico risk group stratification is as follows: low-risk: PSA level of 10 ng/mL or less, a biopsy Gleason score of 6 or less, and 2002 American Joint Committee on Cancer (AJCC) category T1c or T2a; intermediate-risk: PSA level of higher than 10 ng/mL and not more than 20 ng/mL, a biopsy Gleason score of 7, or T2b disease; high-risk: PSA level more than 20 ng/mL, a biopsy Gleason score of 8 to 10, or T2c or greater stage disease. This grouping scheme has been shown to reliably predict prostate-cancer–specific mortality for patients treated with radiation therapy or surgery. By this definition, all patients with locally advanced disease are considered "high-risk"; in addition, patients with high PSA or high Gleason score but low-volume disease are also classified as "high-risk." Although this risk-group classification has been validated in a large multi-institutional setting, it is of such recent vintage that randomized controlled trials (RCTs) that have recently been reported (but designed more than 10-years ago) have not used the D'Amico classification for trial eligibility or stratification. It is important to realize that today's "high-risk" patient is very likely to present with non-locally advanced T-stage disease.

Randomized Controlled Trials of Radiation Therapy and Androgen Deprivation

A number of randomized controlled trials have been completed and reported with adequate follow-up that inform our management of patients with high-risk prostate cancer. There is a large and growing body of evidence to suggest that biochemical outcomes as well as overall survival are improved when radiation therapy is combined with androgen deprivation therapy (ADT). The first of these trials, Radiation Therapy Oncology Group® (RTOG®) 85-31, randomized 977 patients to goserelin acetate indefinitely, initiated at the completion of radiation therapy, or to goserelin acetate at the time of relapse. Inclusion criteria included clinical T3 disease or regional lymphatic involvement or pathologic T3a or T3b disease post-prostatectomy. The most recent update, with a median follow-up period of 7.6 years, reports an improved 10-year absolute survival rate in favor of

immediate indefinite ADT (49% vs 39%, p=0.002). Improvements in local control (LC), distant control (DC), and prostate-cancer–specific mortality (PCSM) were also observed with the addition of immediate ADT.

RTOG 86-10 was a 471 patient randomized trial of radiation therapy with or without 4-months of ADT (goserelin acetate + flutamide). ADT was initiated 2-months prior to radiation and continued concurrently through completion of radiation therapy. Eligibility included patients with bulky T2 (5 x 5 cm), or T3-4 disease with or without positive pelvic lymph nodes. With a median follow-up of 6.7 years, statistically significant improvements favoring the ADT arm were seen with respect to LC, DC, biochemical relapse free-survival (bRFS), and PCSM. Most of this benefit was limited to patients with Gleason scores $\leq$ 6 and patients with bulky disease. In fact, an overall survival (OS) benefit in this low-Gleason-score subset was observed.

The European Organization for Research and Treatment of Cancer (EORTC) completed a randomized trial of 415 patients with high-grade T1-2 or T3/T4 disease. Patients were randomized to radiation therapy with or without 3-years of goserelin acetate (started on day one of radiation). Approximately 90% of the patients had $\geq$T3 disease and 10% had high-grade T1-2 disease. With a median follow-up period of 66 months, the 5-year clinical disease-free survival rate was improved with the addition of ADT compared to radiation therapy alone (74% vs 40%, p=0.0001). The five-year overall survival rate was improved with ADT (78% vs 62%, p=0.0002).

All three studies described above compared radiation alone to radiation therapy combined with ADT. The two studies that included long-term ADT found an overall survival advantage. When short-course ADT was compared to radiation alone, all end-points other than overall survival were improved. The first large randomized trial to address the duration of ADT was RTOG 92-02. This trial accrued 1,554 patients with T2c-4 disease and PSA <150 ng/ml. Fifty-five percent of patients had $\geq$T3 disease with a median PSA of 20 ng/ml. Patients were randomized to either 4-months of ADT given before and concurrent with radiation therapy or the same regimen plus an additional 24-months of adjuvant ADT. With a median follow-up period of 5.8 years, the group assigned to long-term ADT showed improved outcome with respect to disease free survival (DFS), LC, and bRFS, with no overall survival advantage detected (80.0% vs 78.5%, p=0.73). A planned subset analysis of patients with Gleason scores of 8-10 showed a significant improvement in 5-year overall survival with long-term ADT (81% versus 71%, p=0.04). Updated results of this trial will be particularly important.

None of the trials discussed above attempted to answer the question of timing of ADT with respect to radiation therapy. The only RCT designed to systematically address this issue is RTOG 94-13. This was a four-arm randomized (2 x 2 factorial design) trial in which patients were randomized to radiation to the whole pelvis followed by a prostate boost (WP) or prostate only (PO) and were also randomized to neoadjuvant and concurrent hormonal therapy (NCHT) or adjuvant hormonal therapy (AHT) beginning at the completion of EBRT. The total length of ADT was 4-months for all patients. Eligibility for this trial differed from the previous studies in that patients were required to have at least a 15% risk of positive pelvic lymph nodes (LN) based on the following formula: (Risk of +LN=(2/3) PSA + [(GS-6) x 10]). Two-thirds of patients had $\geq$T2c disease. Over 1,300 patients were accrued

and results with a median follow-up time of 59.5 months are available. The 4-year progression-free survival (PFS) rates for WP + NCHT, WP + AHT, PO + NCHT, and PO + AHT were 60%, 49%, 44%, and 50%, respectively (p=0.008). Whole-pelvis radiation therapy plus NCHT was superior to all other arms with respect to PFS at 4-years. No overall survival advantage or difference in the development of distant metastasis has been observed; however, the follow-up period is short and few events have been recorded. This trial supports the use of NCHT over purely adjuvant ADT when the whole-pelvis is treated.

Role of Pelvic Lymph Node Radiation

The following discussion relates to patients with high-risk disease who are at increased risk of positive pelvic nodes without radiographic or histologic evidence of nodal disease. Patients with histologically or radiographically documented lymph node involvement are addressed in the ACR Appropriateness Criteria® Node-Positive Prostate Cancer.

The role of pelvic lymph radiation has been debated for nearly three decades. Until the results of RTOG 94-13 were released, RTOG 77-06 was the only RCT to address this issue. This pre-PSA era study of stage A2 and B patients found no benefit to the addition of elective pelvic lymph node irradiation. It was hypothesized that these patients, some of whom had histologic proof of negative pelvic nodes, were at a low risk of harboring pelvic nodal disease, and as such would not be expected to demonstrate an improved outcome with elective nodal irradiation. RTOG 94-13 revisited this issue in the modern context of PSA staging and ADT, and it included only those patients thought to have at least a 15% likelihood of positive pelvic nodes. It is worth noting that all of the RCTs mentioned above had similar radiation protocols. Initial whole-pelvic fields received between 44 and 50 Gy with final prostate doses ranging from 65-70Gy. Only RTOG 94-13 had an arm that included patients with locally advanced disease without pelvic radiation. Ignoring the timing of hormonal therapy, there was a statistically significant improvement in PFS for those patients that received whole-pelvic radiation compared to those treated with prostate-only radiation (4-year PFS 54% vs 47%, p=0.02). There continues to be debate around this issue, as some retrospective studies suggest that as the dose to the prostate is increased, the magnitude of the benefit of pelvic radiation decreases. This, however, has not been demonstrated in a prospective comparative fashion, and until such time, pelvic irradiation for patients with elevated risk of positive pelvic nodes should be strongly considered.

Dose Escalation with External Beam Radiation Therapy

With the evolution from 2-dimensional treatment planning to 3-dimensional conformal radiation therapy (3DCRT) and IMRT, data have emerged supporting the concept that higher radiation doses will yield better clinical outcomes with acceptable toxicity profiles. The earliest randomized dose-escalation study included only men with locally advanced disease. This study spanned the development of PSA, and thus PSA was not part of the stratification process. All patients were clinically staged T3-4 and all received 50.4 Gy pelvic radiation. Patients were then randomized to either 67.2 GyE or 75.6 GyE via a prostate proton boost. No patients were treated with ADT. With a median follow-up of 61-months, there was no significant difference in OS, PCSM, or DFS. There was,

however, a statistically significant improvement in LC for the 58 patients with poorly differentiated tumors (85% vs 37% at 7-years) favoring the higher dose arm.

Two randomized controlled dose-escalation trials were completed during the PSA era. The more recent one, PROG 95-09, randomized 393 patients with clinically staged T1b-T2b stage disease with PSA values <15 ng/mL to 70.2 GyE vs 79.2 GyE. All patients received 50.4 Gy via photons to the prostate and seminal vesicles and were randomized to an additional 19.8 GyE or 28.8 GyE using conformal protons to the prostate. ADT was not allowed prior to biochemical recurrence. The 5-year bRFS rates were 61% for the conventional-dose arm and 80% for the high-dose arm (p=0.00001). It is important to note that this study did not include any T3 patients and that only 8% would be classified high-risk using the D'Amico classification. Subset analysis by risk group was performed for low- and intermediate-risk groups, and the absolute magnitude of benefit was identical.

The most mature RCT investigated dose from the MD Anderson Cancer Center. The trial randomized 301 patients with T1-3 disease to 70 or 78 Gy. With a median follow-up of 5-years, the reported rates of 6-year freedom from clinical or biochemical failure was 64% and 70%, favoring the high-dose arm. The magnitude of benefit was greatest for patients with PSA values >10 ng/ml (43% vs 62%, p=0.01). Again it should be noted that this study was primarily of intermediate-risk patients, with only 20% of patients entered having clinically staged T3 disease.

Given that PROG 95-09 specifically excluded patients with T3/4 disease and very few of the patients in the study had clinical evidence of extracapsular extension it is problematic to extrapolate the benefit observed with higher doses to men with more advanced disease. On the other hand, in the earlier proton trial at Massachusetts General Hospital, T3-4 patients with high Gleason scores had improved local control with higher doses. It is also important to note that none of the above studies included ADT as part of the initial management, confounding extrapolation to high-risk locally advanced patients treated today.

The use of IMRT is increasing dramatically. This technique allows for significant dose escalation to doses ranging from 76-86 Gy. None of the above studies incorporated IMRT as a means of escalating the dose to the prostate, and randomized trials with adequate follow-up and attention to toxicity will be needed before such high doses can routinely be recommended.

External Beam Radiation Therapy Combined with Brachytherapy

Brachytherapy has been combined with EBRT in the treatment of pelvic cancers for many decades. In patients with locally advanced cervix cancer it is the standard of care. EBRT and brachytherapy have been combined in the treatment of prostate cancer, but the vast majority of published results include only patients with low- and intermediate-risk features. Retrospective data have suggested that monotherapy with LDR brachytherapy is inferior to EBRT or radical prostatectomy (RP) for high-risk patients and has not been advocated for this patients population. A modest amount of data has been published from single institutions

and in small prospective studies on the strategy of combining EBRT with either a low- or high-dose-rate brachytherapy boost for patients with high-risk disease.

One group of researchers described their results with trimodality therapy (neoadjuvant and concurrent ADT, EBRT, and LDR) for 93 patients with locally advanced prostate cancer. This was a single-institution retrospective study. Inclusion criteria were clinical stage $\geq$T2b or PSA >10 ng/mL, or Gleason score of 7. Sixty percent of patients were high-risk, and 30% had clinically staged disease of T2b or greater. Patients were treated with 8-9 months of ADT beginning 2-3 months prior to 40-45 Gy EBRT followed by a 90 Gy palladium-103 implant. With a median follow-up of 45 months, they reported a promising 77% 4-year bRFS rate.

A published series of 132 high-risk men treated with trimodality therapy included men with Gleason scores 8-10, or initial PSA >20 ng/mL, or clinical stage T2c-T3, or positive seminal vesicle biopsy. Gleason scores of 7 were also included if the patients had one other poor risk factor. Treatment included 9-months of ADT with a 90 Gy Pd-103 implant performed 3-months from initiation of hormones. This was followed with 45 Gy EBRT to the prostate. With a median follow-up of 50-months, the 5-year bRFS rate was 86% for the entire cohort and 76% for patients with Gleason scores of 8-10.

Another research group published the results of the only RCT of EBRT with and without a temporary iridium brachytherapy boost in locally advanced disease. The study included 104 patients with T2 and T3 disease and negative staging pelvic lymphadenectomy. Patients randomized to the EBRT alone arm received 66 Gy in 33 fractions and those randomized to the brachytherapy arm received 40 Gy in 20 fractions followed by a 35 Gy temporary Ir-192 implant. EBRT was directed to the prostate and seminal vesicles. ADT was not used until the time of symptomatic progression or the PSA value exceeded 20 ng/mL. With a median follow-up period of 8.2 years, they reported a DFS rate of 71% for the brachytherapy arm vs. 39% for the EBRT alone arm ($p=0.002$). The rate of positive rebiopsy also decreased in the brachytherapy arm (24% vs. 51%). There was no difference in overall survival, although the total number of deaths was low and further follow-up would be needed to detect any difference. The authors concluded that higher radiation doses given over shorter periods of time result in improved local and biochemical control of patients with locally advanced prostate cancer. Limitations of this study include the suboptimal radiation alone dose and the lack of CT planning or 3DCRT.

High-dose-rate (HDR) brachytherapy has also been combined with EBRT. No randomized clinical trial data are available, but large single and multiple institution reports have been published. Researchers at the William Beaumont Hospital published a matched-pair analysis of conformal HDR boost vs EBRT alone for patients with locally advanced prostate cancer. The whole pelvis was treated to 46 Gy followed by a HDR boost. A wide range of HDR fractionation schedules were used with 9.5 Gy x 2 being the most common. The EBRT alone dose was 66 Gy. Seventy-six percent of patients were clinically staged T2b or greater. The authors reported that HDR patients achieved significantly lower PSA nadirs and had improved 5-year bRFS rates compared to EBRT alone patients (67% vs. 44%, $p<0.001$).

Another study reported 10-year results with combined EBRT and HDR brachytherapy. Forty-seven patients with high-risk disease were treated with 36 Gy EBRT to the prostate and four fractions of 5.5-6.0 Gy HDR brachytherapy. ADT was not used. With a median follow-up period of 7.25 years, the bRFS rate for these high-risk patients was 74% at 5-years and 69% at 10-years.

Results of Chemotherapy

Promising results from phase III trials of taxane-based chemotherapy for patients with hormone refractory metastatic prostate cancer have recently been reported. This has led investigators to consider taxanes in the adjuvant setting for patients with high risk of disease progression. A preliminary analysis of RTOG 99-02 was presented in abstract form. This was a RCT for patients with PSA values of 20-100 ng/mL and Gleason scores $\geq$7 or clinical stage $\geq$T2 and GS $\geq$8. All patients received neoadjuvant and long-term ADT and 46.8 Gy to a small pelvic field followed by a prostate boost to 70.2 Gy. Patients were randomized to adjuvant systemic chemotherapy with oral estramustine, oral VP-16 and paclitaxel (TEE), or no additional therapy. This study was closed early after accruing 397 of a planned 1,440 patients secondary to an increased incidence of thromboembolic events in the chemotherapy arm. It is believed that the increased thromboembolic toxicity was caused by the estramustine, and consequently the RTOG is planning another adjuvant chemotherapy study using docetaxel without estramustine (RTOG 0521).

Radical Prostatectomy

The proportion of high-risk prostate cancer patients treated with radical prostatectomy (RP) is small. High-risk patients are being seen with diminishing frequency overall, and radical prostatectomy series tend to have insufficient numbers from which to draw conclusions. A large retrospective experience of men with locally advanced prostate cancer treated with RP in the PSA era was published. Out of 5,652 men who underwent RP, only 842 (15%) had clinical T3 disease. With a median follow-up period of 10.3 years, the 10- and 15-year DFS rates were 73% and 67%, respectively, for clinically staged T3 patients. Of note, 27% of men were overstaged clinically and found to have pathologic T2 disease. Other studies report inferior results when RP is used for locally advanced disease. Two RCTs addressing the role of adjuvant radiation therapy following radical prostatectomy have been reported. The EORTC trial 22911 randomized 1,005 men to observation or immediate adjuvant radiation following prostatectomy. Eligibility included pT3 stage or positive resection margins. The 5-year biochemical progression-free survival rate (bPFR) was only 52.6% in the radical prostatectomy alone arm. Patients with seminal vesicle invasion had a 5-year bPFR survival rate of only 32.4%. Data were presented from the SWOG RCT of adjuvant radiation therapy vs. observation for pathologic T3 patients. The 10-year rate of biochemical relapse-free survival (PSA <0.4 ng/mL) for surgery alone was only 23%.

As with radiotherapy alone, patients treated with radical prostatectomy alone who had clinical T3 disease, Gleason scores of 8-10, and/or pretreatment PSAs of >20 ng/mL have high failure rates. Neoadjuvant ADT has been used with the goal of tumor downstaging to improve margin negativity. The results of an RCT of 3-months vs. 8-months of ADT prior to RP in primarily intermediate-risk patients

found a statistically significant increase in margin negativity in the 8-month ADT arm, with no survival or recurrence data available. While not specifically addressing locally advanced high-risk disease, the RCT from the Scandinavian Prostate Cancer Group is worth mentioning. This trial randomized 695 men between RP and watchful waiting. Seventy-six percent of patients had T2 disease (T3 patients not included), 28% had Gleason scores •7, and the mean pretreatment PSA was 13 ng/mL. The 10-year estimates demonstrated that radical prostatectomy was associated with a statistically significant reduction in all end points investigated, with a relative reduction of 44% in mortality due to prostate cancer, 26% in overall mortality, 40% in the risk of distant metastasis, and 67% in local progression. This is the first randomized clinical trial of a local therapy vs. observation that has demonstrated a statistically significant overall survival advantage to local treatment.

Cryosurgery

Although cryosurgery has received much attention, there have been few reports on high-risk patients with long-term followup. The most recent multi-institutional, retrospective report has been published. No RCT data are available. Patients were considered to be low-risk if the pretreatment PSA was $\leq$10 ng/mL, the Gleason score was <7, and the clinical T-stage was T1-2. All other patients were defined to be high-risk. Biochemical recurrence was defined as a serum PSA >0.4 ng/mL. The median follow-up of the patient population was not provided. Eighty-five percent of men had Gleason scores of 7 or less, and 75% of men had a pretreatment PSA <10 ng/mL. Nearly one-half of the men had nonpalpable disease. Approximately one-half of the men were defined as low-risk according to the definition provided above. More than one-third of the men received ADT prior to cryotherapy (duration unknown). One hundred and six men had PSA information available 12-months following cryotherapy. Seventy-nine of them (75% crude rate) had a PSA <0.4 ng/mL and were considered without evidence of disease. Interestingly, Gleason score (<7 vs $\geq$7), pretreatment PSA ($\leq$10 vs >10) and risk group did not predict for disease status at 12-months. Impotence was reported in 87% of men treated with primary cryotherapy. Urethral sloughing, pelvic pain and scrotal swelling were reported in approximately 5% of the men. Urinary incontinence was reported in approximately 10%. No fistulae or strictures were reported. Other limited reports of primary cryotherapy in high-risk patients are available; however, high-level evidence with appropriate follow-up continues to be lacking.

Conclusion

The available evidence supports the use of androgen deprivation therapy, pelvic lymph node irradiation, and prostate gland doses of greater than 70 Gy in men with high-risk locally advanced prostate cancer. Long-term androgen deprivation (at least 2 years) should be favored over shorter courses. The optimal mechanism of boosting the prostate dose remains unknown, but HDR brachytherapy, LDR brachytherapy, and IMRT are all viable options, and it does not appear that a particular method of prostate boost is superior to another at this time. Future research will be directed at optimizing combined radiation and hormonal therapies as well as incorporating systemic chemotherapeutics in the neoadjuvant, concurrent, and/or adjuvant settings.

Abbreviations

- 2D-CT, two-dimensional-computed tomography based plan
- 3D-CT, three-dimensional-computed tomography based plan
- CAB, combined androgen blockade
- EBRT, external beam radiation therapy
- HDR, high-dose-rate
- IMRT, intensity-modulated radiation therapy
- LDR, low-dose-rate
- LHRH, luteinizing hormone-releasing hormone
- PSA, prostate-specific antigen
- XRT, external-radiation therapy

CLINICAL ALGORITHM(S)

Algorithms were not developed from criteria guidelines.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The recommendations are based on analysis of the current literature and expert panel consensus.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Selection of appropriate radiologic procedures for management of patients with locally advanced (high risk) prostate cancer

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

An American College of Radiology (ACR) Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists, and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those exams generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The

availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the U.S. Food and Drug Administration (FDA) have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about availability, see the "Availability of Companion Documents" and "Patient Resources" fields below.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Lee WR, Papagikoa MA, Roach M III, Anscher MS, Beyer DC, Lawton CA, Merrick G, Michalski JM, Pollack A, Vijayakumar S, Carroll PR, Higano CS, Mauch PM, Expert Panel on Radiation Oncology-Prostate Work Group. Locally advanced (high-risk) prostate cancer. [online publication]. Reston (VA): American College of Radiology (ACR); 2006. 13 p. [49 references]

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

1996 (revised 2006)

GUIDELINE DEVELOPER(S)

American College of Radiology - Medical Specialty Society

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GUIDELINE COMMITTEE

Committee on Appropriateness Criteria, Expert Panel on Radiation Oncology–Prostate Work Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Panel Members: W. Robert Lee, MD; Michael A. Papagikos, MD; Mack Roach III, MD; Mitchell S. Anscher, MD; David C. Beyer, MD; Colleen A. Lawton, MD; Gregory Merrick, MD; Jeff M. Michalski, MD, MBA; Alan Pollack, MD, PhD; Srinivasan Vijayakumar, MD; Peter R. Carroll, MD; Celestia S. Higano, MD; Peter M. Mauch, MD

FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

This guideline updates a previous version: Pollack A, Paryani SB, Hussey D, Perez CA, Beyer DC, Blasko JC, Forman JD, Lee WR, Potters L, Roach M, Scardino P, Schellhammer P, Leibel S. Locally advanced (high-risk) prostate cancer. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000 Jun;215(Suppl):1401-12.

The appropriateness criteria are reviewed annually and updated by the panels as needed, depending on introduction of new and highly significant scientific evidence.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

ACR Appropriateness Criteria® Anytime, Anywhere™ (PDA application). Available from the ACR Web site.

Print copies: Available from the American College of Radiology, 1891 Preston White Drive, Reston, VA 20191. Telephone: (703) 648-8900.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- ACR Appropriateness Criteria®. Background and development. Reston (VA): American College of Radiology; 2 p. Electronic copies: Available in Portable Document Format (PDF) from the American College of Radiology (ACR) Web site.

PATIENT RESOURCES

None available

NGC STATUS

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DISCLAIMER

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Readers with questions regarding guideline content are directed to contact the guideline developer.

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